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ORIGINAL ARTICLE

Diagnostic performance in gastric cancer is higher using endocytoscopy with narrow-band imaging than using magnifying endoscopy with narrow-band imaging

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Abstract

Background For diagnosing gastric cancer, differences in the diagnostic performance between endocytoscopy with narrow-band imaging and magnifying endoscopy with narrow-band imaging have not been reported. We aimed to clarify these differences by analyzing diagnoses made by endoscopists in Japan.

Methods This single-center retrospective cohort study used 106 cancerous and 106 non-cancerous images obtained via both modalities (total, 424 images) for diagnosis. Sixty-one endoscopists with varying experience levels from 45 institutions were included. Diagnostic accuracy, sensitivity, specificity, and positive and negative predictive values were evaluated to determine the diagnostic performance of each modality and compared using the Mann–Whitney *U* test.

Results Among all endoscopists, diagnostic accuracy, sensitivity, positive predictive value, and negative predictive value were higher with endocytoscopy with narrow-band imaging than with magnifying endoscopy with narrow-band imaging (percentage [95% confidence interval]: 78.8% [76.4–83.0%] versus 72.2% [69.3–73.6%], $p < 0.0001$; 82.1% [78.3–85.9%] versus 64.2% [60.4–69.8%], $p < 0.0001$; 88.7% [82.6–90.7%] versus 78.5% [75.4–85.1%], $p = 0.0023$; 79.0% [75.3–80.5%] versus 68.5% [66.4–71.6%], $p < 0.0001$, respectively). In the magnifying endoscopy with narrow-band imaging-trained group, these values were also higher with endocytoscopy with narrow-band imaging than with magnifying endoscopy with narrow-band imaging ($p < 0.0001$, $p = 0.0001$, $p = 0.0143$, and $p < 0.0001$, respectively). Diagnostic accuracy, sensitivity, and negative predictive value were higher with endocytoscopy with narrow-band imaging than with magnifying endoscopy with narrow-band imaging in the magnifying endoscopy with narrow-band imaging-untrained group ($p = 0.0041$, $p = 0.0049$, and $p = 0.0098$, respectively).

Conclusions Diagnostic performance was higher using endocytoscopy with narrow-band imaging than using magnifying endoscopy with narrow-band imaging. Our results may help change the technique used to diagnose gastric cancer.

Keywords Gastric cancer · Endocytoscopy · Magnifying endoscopy · Narrow-band imaging · Diagnosis

Introduction

Gastric cancer is one of the most prevalent cancers and currently has the highest mortality rate [1, 2]. Because of recent advances in endoscopic equipment, the number of cases of gastric cancer detected at an early stage has increased, and the mortality rate has decreased [3]. Additionally, if gastric cancer is detected at a very early stage [4, 5], endoscopic submucosal dissection (ESD) can be performed to avoid surgical resection and preserve the stomach [6, 7]. The diagnostic performance of endoscopy can be improved by performing magnifying endoscopy with narrow-band

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imaging (ME-NBI) in addition to conventional endoscopy [8, 9]. Therefore, ME-NBI is performed as a current standard investigative procedure for diagnosing gastric cancer.

Recently, endocytoscopy (EC) was developed as a form of ultra-magnifying endoscopy [10–12]. With conventional magnifying endoscopy, the magnifying power is approximately 80–100×. However, with EC, magnification of up to approximately 400–500× is possible. This magnification is the same as that used when observing pathological tissue under a microscope. Therefore, similar to histopathology, using the methylene blue and crystal violet staining method, the shapes of cells and the nuclei can be observed by EC. The usefulness of this staining method in EC has been reported in the diagnosis of esophageal cancer [11–13] and colon cancer [10, 12, 14], as well as in the diagnosis of gastric cancer [15–17]. However, the lesion image for diagnosing gastric cancer is unclear because the staining is sparse due to the large amount of mucus production. Furthermore, the staining process takes time, and mucus production is accelerated by staining [15, 17].

EC with narrow-band imaging (EC-NBI), which is a combination of EC without staining and narrow-band imaging, has been reported in the diagnosis of colorectal cancer [18]. Moreover, EC-NBI is statistically significantly more accurate than conventional ME-NBI in the diagnosis of colorectal cancer [18], and EC-NBI may be more useful than ME-NBI in evaluating other organs. If EC-NBI is found to be effective for the diagnosis of gastric cancer, it may be considered a replacement for ME-NBI, which is the standard method in the current diagnostic system. However, to our knowledge, there is no report on the use of EC-NBI for diagnosing gastric cancer. Moreover, it is unclear whether there is a difference in diagnostic performance between ME-NBI and EC-NBI for gastric cancers. Therefore, we aimed to clarify the diagnostic performance of EC-NBI and determine the difference in diagnostic performance between EC-NBI and ME-NBI for gastric cancer by assessing the diagnostic performances of nationwide endoscopists when using each technique.

Materials and methods

Ethical statements

This study was approved by the institutional review board of the Cancer Institute Hospital (approval number: 2019-1032) and performed in compliance with the principles of the Declaration of Helsinki and its later amendments. While recording the data for this study, all personal identifying information was removed. Informed consent for the use of pathological specimens and imaging data for research purposes was obtained from each patient.

Study design

In this single-center retrospective cohort study, the images used were obtained from consecutive cases in which one endoscopist (Y.H.) performed ESD from July 2016 to July 2019. The images and information regarding the cases were extracted from patients' electronic medical records.

Inclusion criteria were cases for which both ME-NBI and EC-NBI were available, and where both images depicted the utmost oral side of the cancerous tissue, as well as the adjacent, non-cancerous tissue. Exclusion criteria were cases in which either ME-NBI or EC-NBI were unavailable or unclear because of the presence of mucus, blood, halation, etc. We also excluded cases with borderline lesions, such as adenoma.

All images were selected by an instructor of the Japan Gastroenterological Endoscopy Society (Y.H.), and a second instructor of the same society (T.H.) confirmed that all images met the inclusion and exclusion criteria. GIF-H260Z and GIF-H290Z videoscopes (Olympus Medical Systems, Tokyo, Japan) were used for ME-NBI. GIF-Y0002 and GIF-H290EC endocytoscopes (Olympus Medical Systems) were used for EC-NBI.

Imaging procedures

ME-NBI was performed at the time of the detailed examination before treatment, and EC-NBI was performed at the time of ESD. Both were taken at the utmost oral side of the cancerous tissue and the adjacent non-cancerous tissue. ME-NBI and EC-NBI were performed at the same site in each case. Figure 1 shows representative images of one case. In accordance with the gastric cancer treatment guidelines [19], the cancerous and non-cancerous segments were confirmed in all cases using post-ESD pathological results as the gold standard.

The endoscopic procedure was performed as follows. ME-NBI was performed before treatment (on a different day). Before the examination, a soft hood (MB-46; Olympus Medical Systems) was mounted on the tip of the endoscope to enable the endoscopist to consistently fix the mucosa at a distance of approximately 2 mm. First, white-light endoscopy was performed. Second, ME-NBI was performed to diagnose the cancerous part and non-cancerous segments. Finally, following indigo carmine spraying, chromoendoscopy was performed.

EC-NBI was performed immediately before treatment (on the same day). A soft hood was not mounted on the tip of the endoscope, since it is necessary to contact the mucosa directly for this technique. EC-NBI was performed to distinguish between the cancerous part and non-cancerous segments.

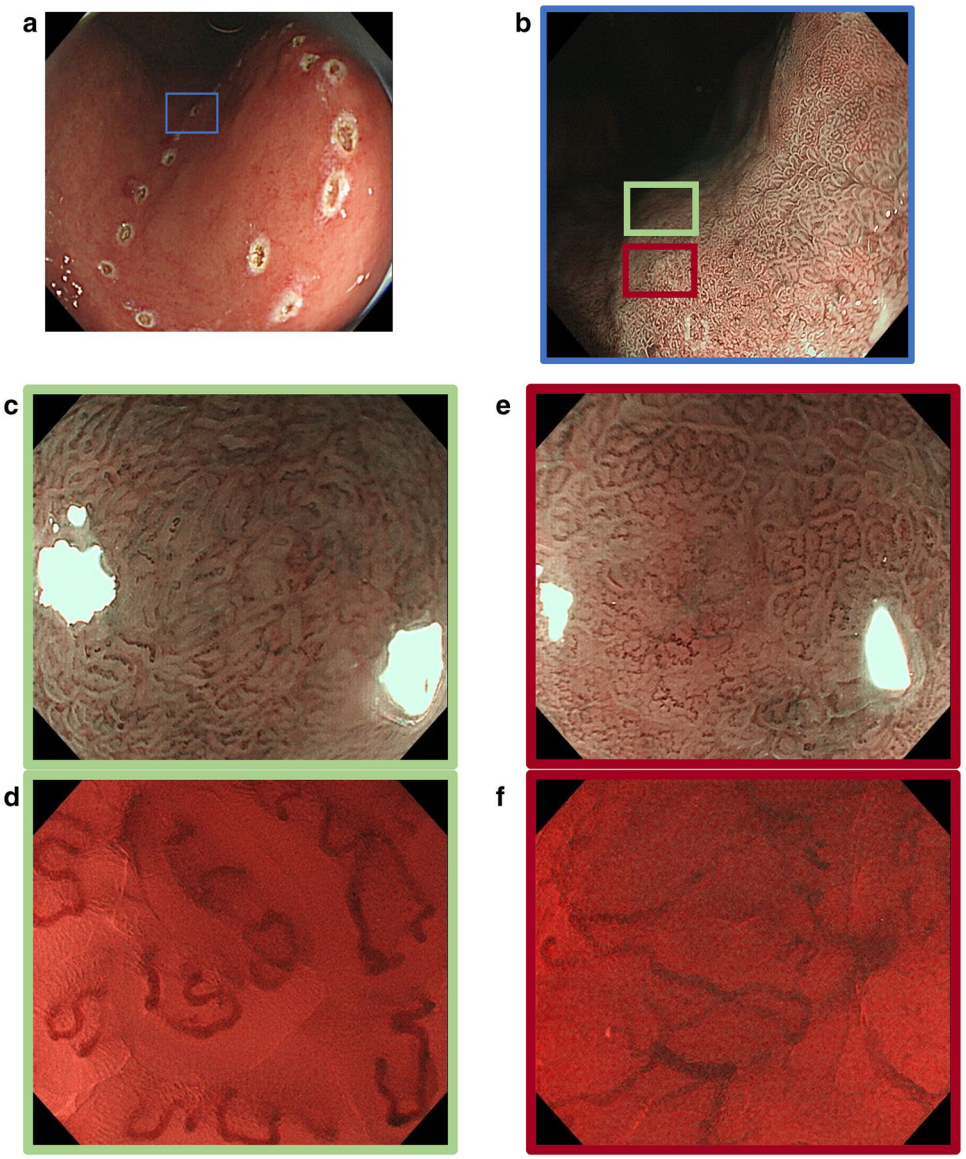


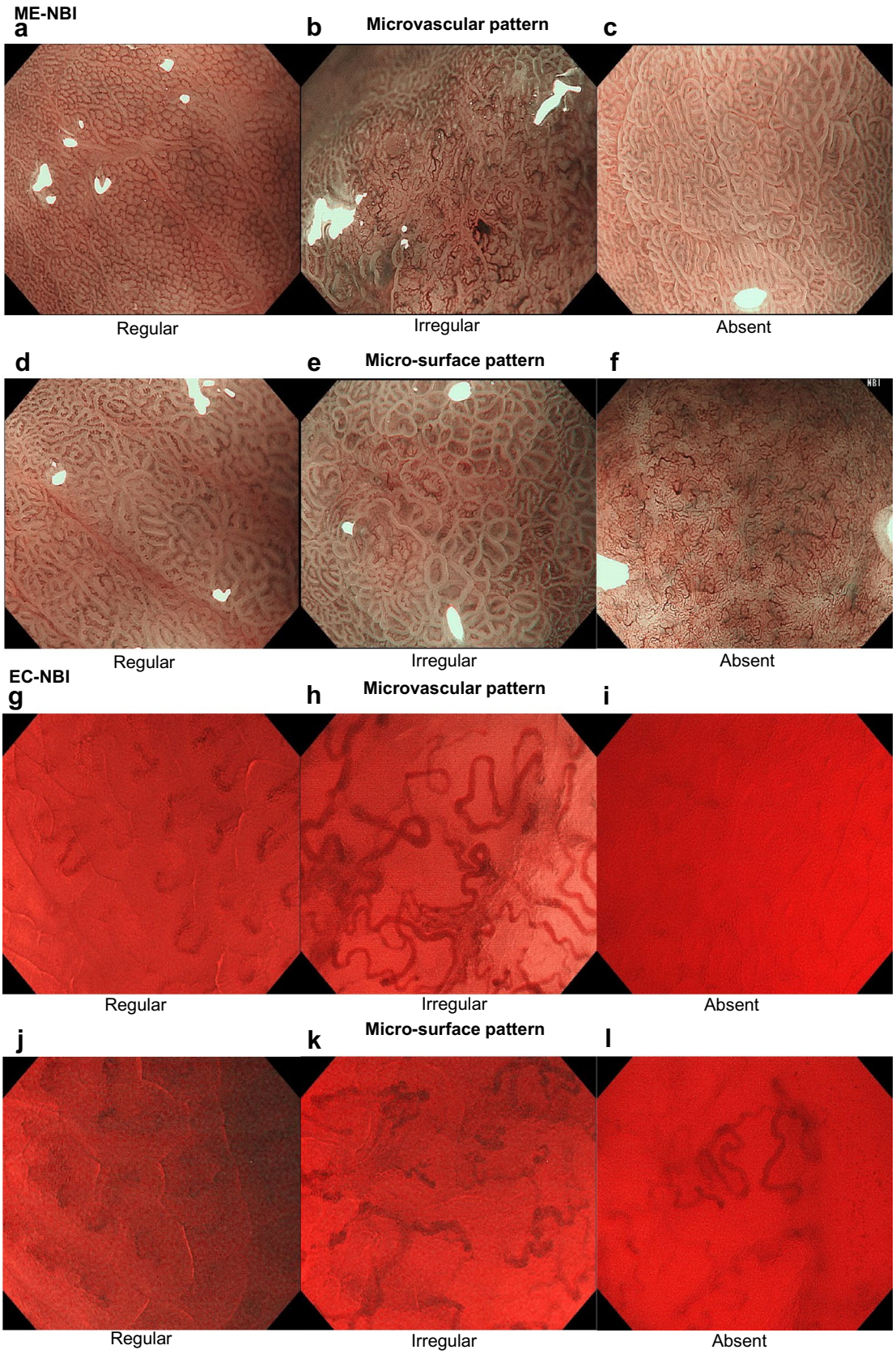
Fig. 1 ME-NBI and EC-NBI of cancerous lesions and non-cancerous tissue. **a** Conventional endoscopy. Blue square, the utmost oral side of the cancerous lesion. **b** The blue square in panel A, enlarged with NBI. Red square, cancerous lesion; green square, non-cancerous tissue. **c** ME-NBI of non-cancerous tissue. **d** EC-NBI of the same site as that in panel C. **e** ME-NBI of a cancerous lesion. The irregular microvascular pattern can be seen from the center of the image to the lower left. **f** EC-NBI of the same site as that in panel E. The irregular microvascular pattern is shown. *ME-NBI* magnifying endoscopy with narrow-band imaging, *EC-NBI* endocytoscopy with narrow-band imaging

Recruitment of endoscopists

We contacted endoscopists in all the facilities in Japan of which our department had email addresses. The endoscopists who agreed to participate in our study made diagnoses based on the images.

The diagnostic method was based on the microvascular (V) and microsurface (S) pattern classification (VS classification) (the ME-NBI diagnostic method), which was proposed by the Japanese Gastroenterological Endoscopy Society as a diagnostic guideline [9, 20]. Before the actual images were supplied to the endoscopists, typical examples of cancerous and non-cancerous ME-NBI and EC-NBI were distributed for their perusal (Fig. 2). Since we could not find reports of such examples of EC-NBI, we selected images for classification of EC-NBI by applying the same classification as for ME-NBI. After reviewing and understanding those images, the endoscopists diagnosed the segments in each actual image as cancerous, non-cancerous, or inconclusive. At the time of diagnosis, the endoscopists were not informed that the ME-NBI and EC-NBI were performed on the same cases or at which sites these were performed.

In addition, information about the endoscopists who made the diagnoses was collected, including years of experience with endoscopy ($> 10, \leq 10$), numbers of cases of endoscopy ($> 10{,}000, \leq 10{,}000$), qualification as a specialist of the Japanese Gastrointestinal Endoscopy Society (qualified, not qualified), specialized training in ME-NBI (yes, no), years of experience with ME-NBI ($> 5, \leq 5$), and experience with EC-NBI (yes, no).


ME-NBI
a
b
Microvascular pattern
c
Regular
Irregular
Absent
d
e
Micro-surface pattern
f
Regular
Irregular
Absent
EC-NBI
g
h
Microvascular pattern
i
Regular
Irregular
Absent
j
k
Micro-surface pattern
l
Regular
Irregular
Absent

◂**Fig. 2** Microvascular pattern and microsurface pattern classification (VS classification). The VS classification is based on the ME-NBI method for distinguishing between cancerous lesions and non-cancerous tissues [9]. If either the microvascular (V) or microsurface pattern (S) is "irregular," the lesion is diagnosed as cancer. We evaluated ME-NBI and EC-NBI by applying this classification. Microvascular pattern (ME-NBI, EC-NBI). Uniform blood vessels (regular) (**a, g**). Blood vessels that expand locally and have different calibers (irregular) (**b, h**). No vascular findings (absent) (**c, i**). Microsurface pattern (ME-NBI, EC-NBI). Uniform surface structure (regular) (**d, j**). Non-uniform surface structure of different sizes (irregular) (**e, k**). No surface structure (absent) (**f, l**). ME-NBI: magnifying endoscopy with narrow-band imaging, EC-NBI: endocytoscopy with narrow-band imaging

Evaluation criteria

This study was performed in accordance with the Standards for the Reporting of Diagnostic Accuracy Studies 2015 guidelines [21]. Diagnostic accuracy, sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated to evaluate and compare the diagnostic performance of ME-NBI and EC-NBI. We defined diagnostic accuracy as follows:

$$\frac{\text{(correctly diagnosed cancerous lesions among all actual cancerous lesions)} + \text{(correctly diagnosed non - cancerous tissues among all actual non - cancerous tissues)}}{\text{total number of images}}$$

The diagnostic ability of ME-NBI can be improved if endoscopists receive ME-NBI training at specialized facilities [22]. Therefore, endoscopists with specialized training in ME-NBI were defined as those who received such training in specialized facilities. Based on the above definition, we categorized endoscopists into two groups (those with and without specialized training in ME-NBI) and compared the diagnostic performance of ME-NBI and EC-NBI for each subgroup. Moreover, we compared the diagnostic performance of ME-NBI and EC-NBI separately in the groups with and without specialized training in ME-NBI.

Statistical analysis

The background characteristics of endoscopists with and without specialized training in ME-NBI were compared using the Fisher exact test. With regard to diagnostic performance, all parameters are presented as medians and interquartile ranges with 95% confidence intervals and were compared using the Mann–Whitney *U* test. When comparing the background characteristics between endoscopists with and without specialized training in ME-NBI, and when

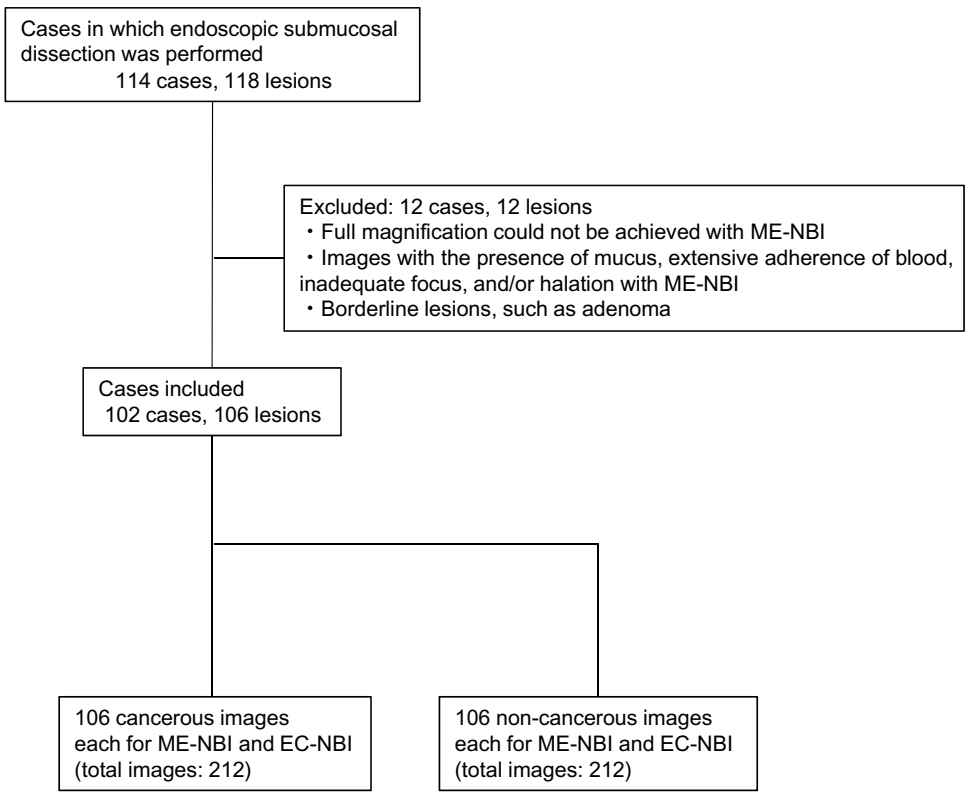


Fig. 3 Patient flow diagram. *ME-NBI* magnifying endoscopy with narrow-band imaging, *EC-NBI* endocytoscopy with narrow-band imaging

Table 1 Background of cases and lesion characteristics

Background of cases	102 cases, 106 lesions
Age (years)	71 (61.8–77) [26–87]
Sex (male/female)	66 (64.7)/36 (35.3)
Location	
Upper third	26 (24.5)
Middle third	59 (55.7)
Lower third	17 (16.0)
Gastric tube	4 (3.8)
Macroscopic type	
Elevated type	15 (14.2)
Flat type	5 (4.7)
Depressed type	83 (78.3)
Complex type	3 (2.8)
Tumor diameter (mm)	14 (9–20.3) [1.5–57]
Depth of invasion	
Intramucosal invasion (pT1a)	90 (84.9)
Submucosal invasion (pT1b)	
< 500 μm	12 (11.3)
≥ 500 μm	4 (3.8)
Ulcerative findings	
Presence	5 (4.7)
Absence	101 (95.3)
Histological type	
Differentiated type	82 (77.4)
Undifferentiated type	24 (22.6)

Data are presented as numbers (%), except for age and tumor diameter, which are expressed as median (interquartile range) [range]

ME-NBI magnifying endoscopy with narrow-band imaging, *EC-NBI* endocytoscopy with narrow-band imaging

Fig. 4 Comparison of the diagnostic performance between ME-NBI and EC-NBI by total endoscopists and by subgroups (diagnostic accuracy, sensitivity, specificity). Data are presented as percentages and expressed as medians (interquartile ranges) [95% CIs]. The Mann–Whitney *U* test was used to compare the variables between ME-NBI and EC-NBI. *ME-NBI* magnifying endoscopy with narrow-band imaging, *EC-NBI* endocytoscopy with narrow-band imaging, *IQR* interquartile range, *95% CI* 95% confidence interval

comparing diagnostic performance between ME-NBI and EC-NBI in all endoscopists, the statistical significance level was set at $p < 0.05$. When comparing diagnostic performance between ME-NBI and EC-NBI within the groups with and without specialized training in ME-NBI, the statistical significance level was set at $p < 0.05/2$, using the Bonferroni method to perform two comparisons in the same population. JMP version 13.2 (SAS® Institute, Cary, NC, USA) was used to perform all the analyses.

Results

Among 114 cases (118 lesions), 102 cases (106 lesions) met the inclusion criteria (Fig. 3). Table 1 shows the background of the cases and lesion characteristics. Moreover, images of 106 non-cancerous segments were obtained. Accordingly, 106 images each were obtained via ME-NBI and EC-NBI (106 cancerous and non-cancerous images, each) and used for the diagnosis (total images: 424).

Table 2 Backgrounds of endoscopists with and without training experience in ME-NBI

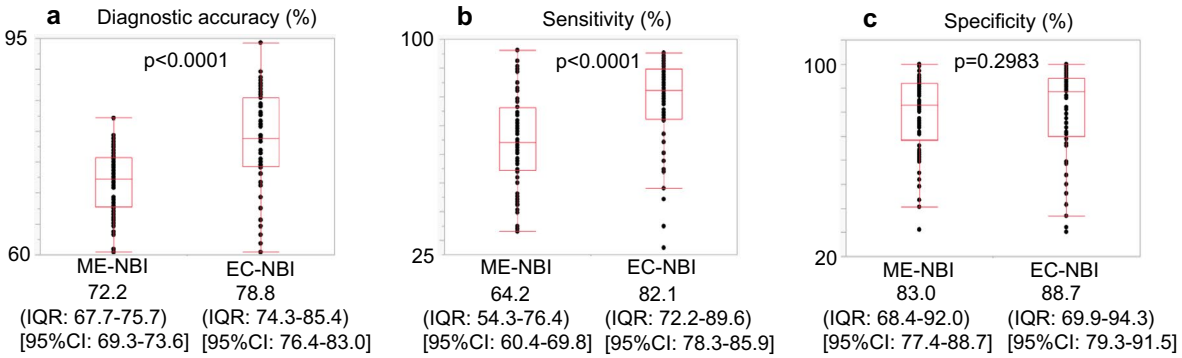
	With specialized training ($n = 33$)	Without specialized training ($n = 28$)	*p* value
Years of experience with endoscopy			0.0004
< 10	18 (54.5)	3 (10.7)	
≥ 10	15 (45.5)	25 (89.3)	
Number of cases of endoscopy			0.0209
< 10,000	21 (63.6)	9 (32.1)	
≥ 10,000	12 (36.4)	19 (67.9)	
Qualification as a specialist of the Japanese Gastrointestinal Endoscopy Society			0.7847
Not Qualified	11 (33.3)	8 (28.6)	
Qualified	22 (66.7)	20 (71.4)	
Years of experience with ME-NBI			0.1238
< 5	14 (42.4)	18 (64.3)	
≥ 5	19 (57.6)	10 (35.7)	
Experience with EC-NBI			0.0597
No	26 (78.8)	27 (96.4)	
Yes	7 (21.2)	1 (3.6)	

Data are presented as numbers (%)

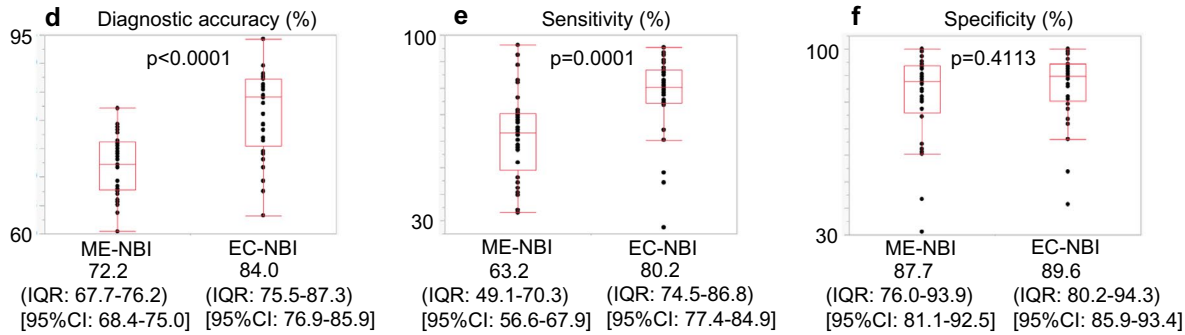
The Fisher exact test was used to compare the background between endoscopists with and without training experience in ME-NBI

ME-NBI magnifying endoscopy with narrow-band imaging, *EC* endocytoscopy with narrow-band imaging

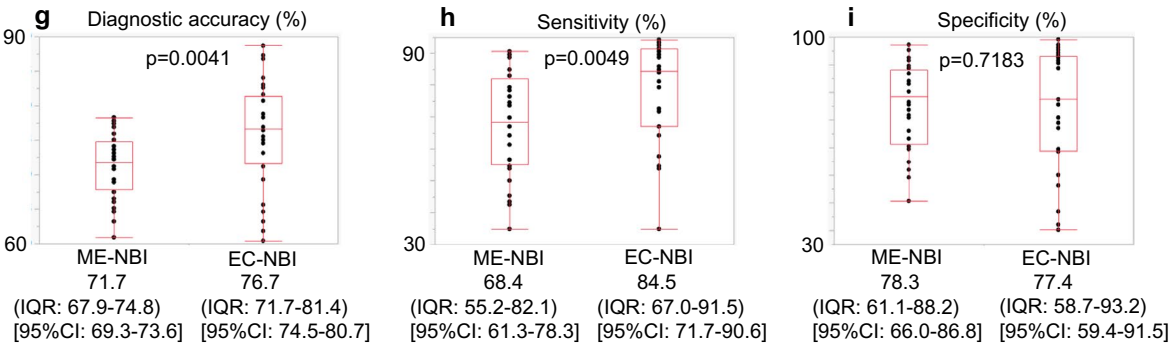
Comparison between ME-NBI and EC-NBI by total endoscopists



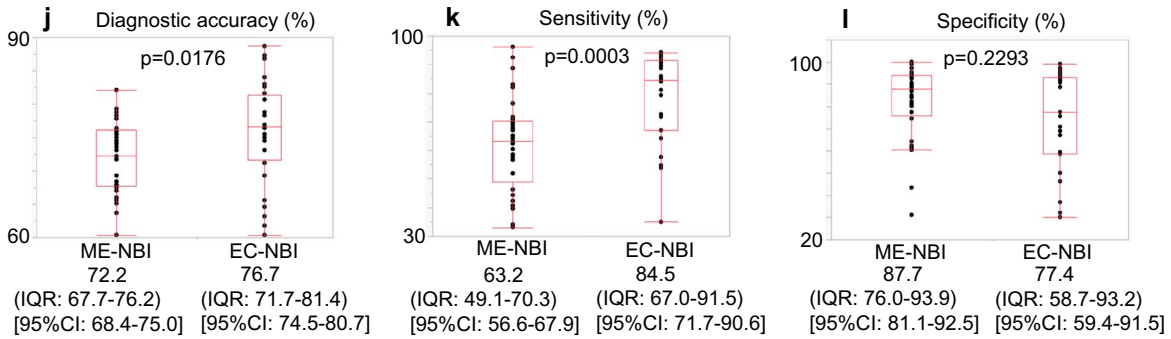
Comparison between ME-NBI and EC-NBI by endoscopists with specialized training in ME-NBI



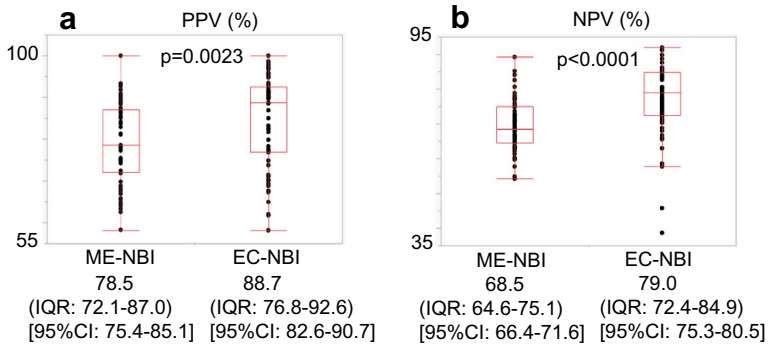
Comparison between ME-NBI and EC-NBI by endoscopists without specialized training in ME-NBI



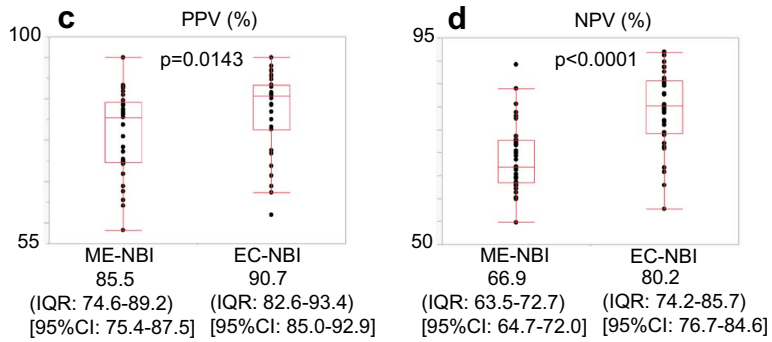
Comparison of each modality in the group with specialized training in ME-NBI for ME-NBI and the group without specialized training in ME-NBI for EC-NBI-



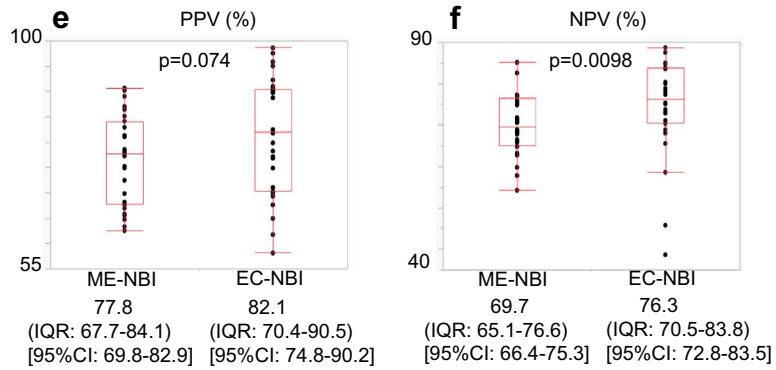
Comparison between ME-NBI and EC-NBI by total endoscopists



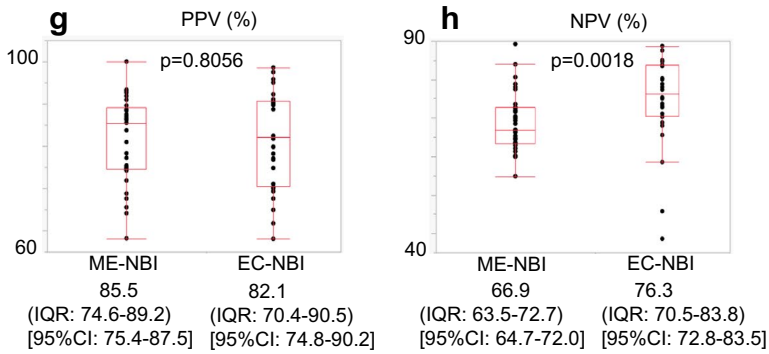
Comparison between ME-NBI and EC-NBI by endoscopists with specialized training in ME-NBI



Comparison between ME-NBI and EC-NBI by endoscopists without specialized training in ME-NBI



Comparison of each modality in the group with specialized training in ME-NBI for ME-NBI and the group without specialized training in ME-NBI for EC-NBI



◂**Fig. 5** Comparison of the diagnostic performance between ME-NBI and EC-NBI by total endoscopists and by subgroup (positive and negative predictive value). Data are presented as percentages and expressed as medians (interquartile ranges) [95% CIs]. The Mann–Whitney *U* test was used to compare all variables between ME-NBI and EC-NBI. *ME-NBI* magnifying endoscopy with narrow-band imaging, *EC-NBI* endocytoscopy with narrow-band imaging, *PPV* positive predictive value, *NPV* negative predictive value, *IQR* interquartile range, *95% CI* 95% confidence interval

Online Resource 1 shows the background of endoscopists, by specialized training. Sixty-one endoscopists from 45 institutions participated. Proportions of endoscopists with ≥ 10 years of experience with endoscopy, those with experience of ≥ 10,000 cases of endoscopy, those who were qualified as specialists of the Japanese Gastrointestinal Endoscopy Society, those with specialized training in ME-NBI, those with ≥ 5 years of experience with ME-NBI, and those with experience with EC-NBI were 65.6, 50.8, 68.9, 54.1, 34.4, and 13.1%, respectively. The group with specialized training in ME-NBI had fewer years of experience in endoscopy and fewer cases of endoscopy than the group without specialized training in ME-NBI had (Table 2).

Figures 4a–i and 5a–f show a comparison of the diagnostic performance between ME-NBI and EC-NBI by total endoscopists, as well as within groups with and without specialized training in ME-NBI. Among total endoscopists, and among those with specialized training in ME-NBI, diagnostic accuracy, sensitivity, PPV, and NPV were higher for EC-NBI than for ME-NBI (all $p < 0.01$, and all $p < 0.02$, respectively). In the group without specialized training in ME-NBI, diagnostic accuracy, sensitivity, and NPV were higher for EC-NBI than for ME-NBI (all $p < 0.01$).

In addition, we compared the diagnostic performance of each modality for ME-NBI in the group with specialized training in ME-NBI, with those for EC-NBI in the group without specialized training in ME-NBI (Figs. 4j–l and 5g–h). Diagnostic accuracy, sensitivity, and NPV were higher for EC-NBI in the group without specialized training in ME-NBI, than for ME-NBI in the group with specialized training in ME-NBI (all $p < 0.02$).

Discussion

Here, we clarified the diagnostic performance of EC-NBI in gastric cancer and compared the diagnostic performance of ME-NBI and EC-NBI by endoscopists with different levels of experience. To our knowledge, this is the first study to perform such analyses.

For all endoscopists, diagnostic accuracy, sensitivity, PPV, and NPV were higher for EC-NBI than for ME-NBI. Even when we divided endoscopists into groups with and without specialized training in ME-NBI, the diagnostic performance was higher for EC-NBI than for ME-NBI in each group. The reason for this finding may be that EC-NBI can be performed at a higher magnification than ME-NBI. Therefore, changes in vessels and surface structure due to cancerous invasion can be observed in more detail, which increases the accuracy of diagnosis. Moreover, before the endoscopists started making diagnoses based on the actual images, typical cancerous and non-cancerous examples of ME-NBI and EC-NBI were distributed for their perusal. Since we could not find reports of such examples of EC-NBI, we selected EC-NBI results and classified them in the same way as for ME-NBI. We found that the diagnostic method used for ME-NBI can also be applied to EC-NBI. Hence, our findings suggest that EC-NBI can be used to diagnose cancerous and non-cancerous tissues with a higher accuracy than ME-NBI in clinical practice.

In a previous study, diagnostic performance was demonstrated to be improved by performing ME-NBI in addition to conventional endoscopy [8]. However, because the endoscopists in that study were specialists in making diagnoses by ME-NBI, the effect of ME-NBI in addition to conventional endoscopy for endoscopists without specialized training in ME-NBI is unknown. This study has a couple of strengths. First, we showed that EC-NBI was even more useful than ME-NBI for such diagnoses. Second, EC-NBI was also shown to be useful for endoscopists without specialized training in ME-NBI.

Although it takes substantial effort to acquire diagnostic ability with ME-NBI, training over the Internet is reportedly useful for improving such ability [22]. However, e-learning and specialized facilities for ME-NBI training are not available to all endoscopists. Indeed, in this study, the majority of endoscopists with ≥ 10 years of experience in endoscopy and ≥ 10,000 cases of endoscopy had not received specialized training in ME-NBI. Furthermore, although endoscopists did not receive EC-NBI training in specialized facilities, diagnostic performance with EC-NBI was higher in the group without specialized training in ME-NBI, than with ME-NBI in the group with specialized training in ME-NBI. Thus, endoscopists without specialized training may be able to make more accurate diagnoses with EC-NBI, than those with specialized training in ME-NBI make with ME-NBI. This result is one of the strong points of EC-NBI observed in this study. However, because the group without specialized training in ME-NBI had more experience in endoscopy and had performed a higher number of endoscopies than the group with such specialized training, this result may not be applicable to beginners in the field of endoscopy. Therefore, to determine the outcomes for endoscopy beginners, further studies are necessary.

Diagnosing gastric cancer in the stomach using the staining method for EC has been reported previously [15–17]. However, the image of the lesion becomes unclear as

staining is sparse due to the large amount of mucus production; furthermore, it takes time to stain, and mucus production is accelerated by the staining [15, 17]. In this study, EC-NBI did not require staining, circumventing the abovementioned problems. Moreover, staining methods have the drawback of requiring pathological knowledge for the evaluation of nucleic and cellular structure. Since EC-NBI does not require pathological knowledge, it allows more endoscopists to make a diagnosis.

Additionally, although it is necessary to use a soft hood to observe the target lesion at a distance with ME-NBI, it is possible to observe the target lesion closely with EC-NBI without the need for a soft hood. Therefore, it is less susceptible to respiratory fluctuations and body movements. Indeed, eight lesions that were excluded from the study were excluded owing to inadequate ME-NBI, and none were excluded due to inadequate EC-NBI (four other lesions were excluded as borderline lesions).

There are some limitations to this study. First, it had an observational design and was conducted at a single center. Second, bias may be present because this study did not include the original diagnosis at the time of endoscopy. Third, borderline lesions such as adenomas and erosive or depressed lesions that are difficult to distinguish as cancerous or non-cancerous were not included in the study, as the non-cancerous part was adjacent to the cancerous part on its oral side. Fourth, only 24 of the cases were of undifferentiated-type cancers. Finally, all the images were of cases in which ESD was performed, and this study did not include cases in which gastric cancer was overlooked.

Despite these limitations, this study was based on consecutive cases of one doctor from a hospital that specializes in cancer, and the diagnostic performance of many endoscopists was evaluated. Moreover, since 61 endoscopists from 45 facilities all over Japan participated and the median was used to evaluate the diagnostic performance, we expect that this study's results are generalizable.

Biopsies are usually required to detect cancers following screening tests conducted using endoscopy [4, 5]. To determine whether biopsy is required, endoscopic differentiation of cancerous and non-cancerous lesions is necessary to a certain extent. Therefore, we believe that EC-NBI will be a useful test for cancer screening.

In future, to prove the usefulness of EC-NBI, we plan to propose a multicenter prospective study to clarify the difference in diagnostic performance by randomizing the use of EC-NBI or ME-NBI and performing screening in clinical practice. In such a study, we will also increase the included number of undifferentiated-type cancers and include borderline lesions. Cases in which gastric cancer are overlooked and in which ESD is not performed would be included. Ultimately, the results of the study presented here will serve as valuable data.

In conclusion, we clarified that the diagnostic performance of EC-NBI in gastric cancer was higher than that of ME-NBI when comparing results from all endoscopists involved in the study. Moreover, it was considered that the diagnostic performance of EC-NBI in the group without specialized training in ME-NBI was sufficiently accurate. This study's results may initiate a change in preference of the technique used to diagnose gastric cancer, from ME-NBI to EC-NBI, and contribute to the improvement of the diagnostic accuracy for gastric cancer. We suggest that EC-NBI will be useful in the diagnosis of gastric cancer in clinical practice.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Human rights statement All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964 and later versions.

Informed consent Informed consent to be included in the study, or the equivalent, was obtained from all patients.

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